

## ELECTRONICALLY FILED

<b>PETITION FOR CERTIFICATE OF CORRECTION</b>  Address to: Mail Stop Certificate of Correction Branch Commissioner for Patents P.O. Box 1450 Alexandria, VA 22313-1450	Attorney Docket	STAN-130
	First Named Inventor	BRIESEWITZ, ROGER
	Patent Number	6,887,842
	Issue Date	May 3, 2005
	Application Number	09/716,841
	Filing Date	November 17, 2000
	Title: <i>“Modulating a Pharmacokinetic Property of a Drug by Administering a Bifunctional Molecule Containing The Drug”</i>	

Sir:

Transmitted herewith for filing is a Certificate of Correction for the above-identified patent. In column 1, lines 14-19, please delete the header “Acknowledgement” and the paragraph immediately following beginning with “This invention” to and ending “in this invention.” This acknowledgement was entered in error. This patent referenced herein was not supported by any government grants.

The \$100 fee set forth under 37 C.F.R. § 1.20 is enclosed. The Commissioner is hereby authorized to charge any additional fees which may be required by this paper, or to credit any overpayment, to Deposit Account No. 50-0815 order number STAN-130.

Respectfully submitted,

BOZICEVIC, FIELD & FRANCIS LLP

Date: December 9, 2011

By: /Bret E. Field, Reg. No. 37,620/  
 Bret E. Field  
 Registration No. 37,620

BOZICEVIC, FIELD & FRANCIS LLP  
 1900 University Avenue, Suite 200  
 East Palo Alto, California 94303  
 Telephone: (650) 327-3400  
 Fax: (650) 327-3231

1

# MODULATING A PHARMACOKINETIC PROPERTY OF A DRUG BY ADMINISTERING A BIFUNCTIONAL MOLECULE CONTAINING THE DRUG

## CROSS REFERENCE TO RELATED APPLICATIONS

Pursuant to 35 U.S.C. § 119 (e), this application claims priority to the filing date of the U.S. Provisional Patent Application Ser. No. 60/166,633 filed Nov. 19, 1999, the disclosure of which is herein incorporated by reference.

## ~~ACKNOWLEDGMENT~~

~~This invention was made with United States Government support under Grant No. CA39612 awarded by National Institutes of Health. The United States Government has certain rights in this invention.~~

## INTRODUCTION

### 1. Technical Field

The field of this invention is pharmacology.

### 2. Background of the Invention

Any chemical agent that affects any process of living is a drug. Drugs are a critical tool for health care practitioners, as they are used in the prevention, diagnosis and treatment of disease. Because of their criticality to the health care profession, annual world investment into the research and development of new chemical agents with therapeutic potential reaches into the billions of dollars. As a result, a large number of drugs have been developed to date and new chemical agents having potential therapeutic utility are frequently discovered. Chemical agents that find, or have found, use as drugs include naturally occurring and synthetic small molecules, as well as larger molecules, such as proteinaceous compounds.

A major challenge in the development of drugs is the predictable modulation of pharmacokinetic properties. Major pharmacokinetic parameters that effect the ability of a particular drug to treat a given condition include: the drug half-life, the hepatic first-pass metabolism of the drug, the volume of distribution of the drug, the degree of albumin binding of the drug, etc. Each of the above parameters can have a profound effect on the efficacy of a given drug agent.

As such, of great interest to the pharmaceutical industry and related fields would be the development of a methods for predictably modulating one or more of these pharmacokinetic properties so as to improve a given drug, e.g. the efficacy of a given drug. Of particular interest would be the development of a method which retained the small molecule nature of the drug, so as to retain the advantages of small molecule compounds with respect to drug delivery.

### Relevant Literature

Patent publications of interest include: WO 91/01743; WO 94/18317; WO 95/02684; WO 95/10302; WO 96/06111; WO 96/12796; WO 96/13613; WO 97/25074; WO 97/29372; WO 98/11437; WO 98/47916; U.S. Pat. No. 5,714,142; U.S. Pat. No. 5,830,462; U.S. Pat. No. 5,843,440; and U.S. Pat. No. 5,871,753. References of interest include: Briesewitz et al., Proc. Nat'l Acad. Sci. USA (March 1999) 96: 1953-1958; Clardy, Proc. Nat'l Acad. Sci. USA (March 1999) 1826-1827; Crabtree & Schreiber, Elsevier Trends Journal (November 1996) 418-422; Spencer et al., Curr. Biol. (July 1996) 6:839-847; Spencer et al., Science (1993) 262: 1019; Chakraborty et al., Chem. & Biol. (March 1995) 2:157-161; Ho et al., Nature (1996) 382: 822; Riviera et al.,

2

Nature Medicine (1996) 2: 1028; Klemm et al., Current Biology (1997) 7: 638; Belshaw et al., Proc. Nat'l Acad. Sci. USA (1996) 93: 4604; Livnah et al., Science (1996) 273: 464; Johnson et al., Chemistry and Biology, (1997) 4: 939; Garboczi et al., Nature (1996) 384:134; Kissenger et al., Nature (1995) 378:641; Griffith et al., Cell (1995) 82: 507; Choi et al., Science (1996) 273:239. Also of interest are Kramer et al., J. Biol. Chem. (1992) 267:18598-18604; and Varshavsky, Proc. Nat'l Acad. Sci. USA (March 1998) 95: 2094-2099; Varshavsky, Proc. Nat'l Acad. Sci. USA (April 1995) 92:3663-3667; and Mu et al., Biochem. Biophys. Res. Comm. (1999)255:75-79.

## SUMMARY OF THE INVENTION

Bifunctional molecules and methods for their use are provided. The subject bifunctional molecules are conjugates of a drug moiety and a pharmacokinetic modulating moiety, where these two moieties are optionally joined by a linking group. The bifunctional molecules are further characterized in that they exhibit at least one modulated pharmacokinetic property upon administration to a host as compared to a free drug control. The subject bifunctional molecules find use in a variety of therapeutic applications.

## DEFINITIONS

The term "bifunctional molecule" refers to a non-naturally occurring molecule that includes a pharmacokinetic modulating moiety and a drug moiety, where these two components may be covalently bonded to each other either directly or through a linking group.

The term "drug" refers to any active agent that affects any biological process. Active agents which are considered drugs for purposes of this application are agents that exhibit a pharmacological activity. Examples of drugs include active agents that are used in the prevention, diagnosis, alleviation, treatment or cure of a disease condition.

By "pharmacologic activity" is meant an activity that modulates or alters a biological process so as to result in a phenotypic change, e.g. cell death, cell proliferation etc.

By "pharmacokinetic property" is meant a parameter the describes the disposition of an active agent in an organism or host. Representative pharmacokinetic properties include: drug half-life, hepatic first-pass metabolism, volume of distribution, degree of blood serum protein, e.g. albumin, binding, etc.

By "half-life" is meant the time for one-half of an administered drug to be eliminated through biological processes, e.g. metabolism, excretion, etc.

By "hepatic first-pass metabolism" is meant the propensity of a drug to be metabolized upon first contact with the liver, i.e. during its first pass through the liver.

By "volume of distribution" is meant the distribution and degree of retention of a drug throughout the various compartments of an organisms, e.g. intracellular and extracellular spaces, tissues and organs, etc.

By "degree of blood serum binding" is meant the propensity of a drug to be bound by a blood serum protein, such as albumin, in manner such that the activity of the drug is substantially dissipated if not abolished. This property is also referred to herein as the blood serum binding effect. In those embodiments where the blood serum protein is albumin, this property is also referred to as the albumin binding effect.

The term "efficacy" refers to the effectiveness of a particular active agent for its intended purpose, i.e. the ability of a given active agent to cause its desired pharmacologic effect.

## UNITED STATES PATENT AND TRADEMARK OFFICE CERTIFICATE OF CORRECTION

Page 1 of 1

PATENT NO. : 6,887,842  
APPLICATION NO.: 09/716,841  
ISSUE DATE : May 3, 2005  
INVENTOR(S) : BRIESEWITZ, ROGER

It is certified that an error appears or errors appear in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

**In the Specification:**

- \* In column 1 line 14: Please delete the header "Acknowledgement" and paragraph beginning with "This invention" to and ending "in this invention."

MAILING ADDRESS OF SENDER (Please do not use customer number below):

**BOZICEVIC, FIELD & FRANCIS LLP**  
1900 University Avenue, Suite 200  
East Palo Alto, California 94303